REMARKS

Upon entry of the foregoing amendment, claims 1-52 are pending in the application, with claims 1-27 withdrawn by the Examiner under 35 U.S.C. § 121. Currently, claims 28-44 are objected to for the use of abbreviated language TRAIL as the means of identifying the claimed polypeptide, and claim 32 is objected to for the use of the language "substantially." Claims 28-44 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly not complying with the enablement requirement. Also, claims 28-44 stand rejected as allegedly obvious under 35 U.S.C. § 103.

As amended, claims 28-41 describe a composition for treating cancer by inducing cell death in cancer cells comprising an effective amount of a Tumor necrosis factor α - Related apoptosis Inducing Ligand (TRAIL) polypeptide comprising a wild-type TRAIL polypeptide having the amino acid sequence SEQ ID NO: 1, or the biological equivalent thereof, and an antiprogestin in a pharmaceutical carrier, wherein an effective amount comprises sufficient TRAIL polypeptide and antiprogestin to induce apoptosis in at least a portion of the cancer cells exposed to the composition. Also, as amended, claims 42-44 describe a kit that comprises a pharmacologically effective amount of a Tumor necrosis factor α - Related apoptosis Inducing Ligand (TRAIL) polypeptide comprising a wild-type TRAIL polypeptide having the amino acid sequence SEQ ID NO: 1, or the biological equivalent thereof, packaged in a sterile container; a pharmacologically effective amount of an antiprogestin packaged in a sterile container; (c) at least one aliquot of a pharmaceutical carrier; and (d) instructions for application of the TRAIL polypeptide and the antiprogestin to a patient having cancer. Support for the amendment is found in the specification where it is defined that TRAIL (Tumor necrosis factor α - Related apoptosis Inducing Ligand) is a 281 amino acid type II transmembrane protein (e.g., specification at page 16, lines 22-28, and page 26, lines 14-15, describing the TRAIL polypeptide used). Also, new claims 45-52 are supported by the specification at page 13, line 29 to page 14, line 25. The specification is amended to refer to the sequence of wild-type TRAIL (SEQ ID NO: 1) as suggested by the Examiner. Additional amendments clarify the syntax or correct typographical errors in the text. Accordingly, no new matter is added by the amendments to the specification or the claims.

The Objection to the Claims is Traversed or Rendered Moot

The Examiner objected to the claims for the use of the abbreviated language "TRAIL" and stated that a full name of TRAIL, as well as a physical and/or functional characteristic is required. Independent claims 28, 30, and 42 have been amended to include the full name for TRAIL - Tumor necrosis factor α - Related apoptosis Inducing Ligand and to describe that the TRAIL polypeptide is a wild-type TRAIL polypeptide having the amino acid sequence SEQ ID NO: 1, or the biological equivalent thereof. Thus, Applicants respectfully request that the objection be withdrawn.

The Rejection of Claim 32 Under 35 U.S.C. 112, Second Paragraph, is Traversed or Rendered Moot

The Examiner objected to the use of the term "substantially" in claim 32. Applicant respectfully traverses the objection. Use of the term substantially is provided for by MPEP 2173.05(b) describing that the term "substantially equal" is definite because "one of ordinary skill in the art would know what is meant by 'substantially equal.'" MPEP 2173.05(b) *citing Andrew Corp. v. Gabriel Electronics*, 847 F.2d 819 (Fed. Cir. 1988). Similarly, one of ordinary skill in the art would know that having TRAIL polypeptide and Mifepristone released "substantially simultaneously" accounts for very small differences in release of the two compounds that may occur in a particular formulation, but where on average, the release of the two compounds is for practical purposes, simultaneous. Thus, Applicant respectfully requests that the objection be withdrawn.

The Rejection of the Claims Under 35 U.S.C. 112, First Paragraph, is Traversed or Rendered Moot

A. Incorporation of Essential Material

The Examiner rejected claims 28-44 as allegedly not complying with the enablement requirement under 35 U.S.C. 112, first paragraph. Thus, the Examiner stated that TRAIL is an essential material for the claimed composition, and thus, may not be incorporated by reference to a foreign application or patent, or to a publication. Applicant respectfully notes that the physical characteristics of TRAIL are described in

the specification. Thus, it is described that TRAIL (Tumor necrosis factor α – Related Apoptosis Inducing Ligand) is a 281 amino acid type II transmembrane protein also referred to as Apo2L. The TRAIL used in the experiments was obtained from a commercial supplier (Biomol Research laboratories, Inc., Pymouth Meetings, PA) and thus was, and is currently, available to the public. The Specification at page 26, line 16. Thus, for the record, Applicant respectfully asserts that the disclosure of TRAIL as provided in the specification is enabling.

Applicant has, however, amended the specification to further describe that the TRAIL used to induce apoptosis is TRAIL polypeptide having a sequence of wild-type TRAIL reported in Pitti et al., J. Biol. Chem., 271:12687-12690 (1996) (i.e., GenPept Accession No. AAB01233), and described by SEQ ID NO. 1, submitted herewith, or a biological equivalent thereof.

Applicant further provides herewith a declaration executed by the Applicant, stating that the amendatory material consists of the same material incorporated by reference in the referencing application.

B. Scope

The Examiner further rejected claims 28-44 under 35 U.S.C. 112, first paragraph as allegedly going beyond the scope of what was enabled by the specification. Thus, the Examiner stated that "the specification, while enabling for a composition comprising a wild type TRAIL polypeptide and an antiprogestin for treating cancer, does not reasonably provide enablement for a composition comprising any TRAIL polypeptide, such as a variant TRAIL, or a TRAIL polynucleotide and an antiprogestin for treating cancer." Office Action at page 5.

As amended, claims 28-41 describe a composition for treating cancer by inducing cell death in cancer cells comprising an effective amount of a Tumor necrosis factor α - Related apoptosis Inducing Ligand (TRAIL) polypeptide comprising a wild-type TRAIL polypeptide having the amino acid sequence SEQ ID NO: 1, or the biological equivalent thereof, and an antiprogestin in a pharmaceutical carrier, wherein an effective amount comprises sufficient TRAIL polypeptide and antiprogestin to induce apoptosis in at least a portion of the cancer cells exposed to the composition. Also, as amended, claims 42-44 describe a kit that comprises a pharmacologically effective amount of a Tumor necrosis

factor α - Related apoptosis Inducing Ligand (TRAIL) polypeptide comprising a wild-type TRAIL polypeptide having the amino acid sequence SEQ ID NO: 1, or the biological equivalent thereof, packaged in a sterile container; a pharmacologically effective amount of an antiprogestin packaged in a sterile container; (c) at least one aliquot of a pharmaceutical carrier; and (d) instructions for application of the TRAIL polypeptide and the antiprogestin to a patient having cancer.

The amendment of the claims clarifies that it is wild type TRAIL polypeptide having the amino acid sequence SEQ ID NO: 1, or a biologically equivalent thereof, that is used in treating cancer in combination with an antiprogestin. Wild type TRAIL may be purchased commercially, or produced by expression of the nucleic acid sequence that encodes TRAIL (e.g., Pitti et al., J. Biol. Chem., 271:12687-12690, 1996) in a cell culture system. Biologically equivalent TRAIL polypeptides are those polypeptides that have substitutions, additions, or deletions (e.g., fragments of TRAIL) such that the biological activity is the same. Such biologically equivalent peptides may be evaluated using the assay systems described in the specification (e.g., Examples 2-10). Thus, Applicant respectfully asserts that the claims, as amended, are enabled under 35 U.S.C. § 112, first paragraph, and respectfully requests that the rejection be withdrawn.

The Rejection of the Claims Under 35 U.S.C. 103 is Traversed or Rendered Moot

The Examiner rejected claims 28-44 under 35 U.S.C. 103(a) as being allegedly unpatentable over Bonavida, B. et al., 1999, Oncology 15(4):793-802 (hereinafter "Bonavida") or Yu et al, 2000, Cancer Res., 60:2384-2389 (hereinafter "Yu"), or Gliniak, B., et al., 1999, Cancer Res., 59:6153-6158M (hereinafter "Gliniak"), in view of Fathy El Etreby et al., 2000, The Prostate 42: 99-106 (hereinafter "Fathy El Etreby"), or Kiode, S.S., et al., J. Reproductive Medicine, 1998, 43:551-560 (hereinafter "Kiode").

The Examiner cites Bonavida, Yu, and Gliniak as describing the use of TRAIL to induce apoptosis in tumor cells. The Examiner stated that Bonavida describes that human mammary adenocarcinaoma cells in vivo and several tumor cells are sensitive to TRAIL-mediated apoptosis, and that tumor cells may develop resistance to TRAIL, and that such resistance may possibly be reversed by combining TRAIL with other drugs. Also, the Examiner stated that Yu teaches that TRAIL induces cell death in androgen-independent

prostate cancer cells PC-3 and DU145, and that Gliniak teaches that TRAIL can induce apoptosis in a wide variety of transformed human cells in vitro, and that colon carcinoma cells display sensitivity to TRAIL in vivo that parallel their sensitivity to TRAIL-induced apoptosis in vitro. Office Action at page 12-13. The Examiner cites the other two references, Fathy El Etreby and Koide, as describing the use of Mifepristone to treat non-prostate cancer (Koide) and prostate cancer (Fathy El Etreby). Office Action at page 13-14.

The Federal Circuit has stated that "[i]n order to render a claimed apparatus or method obvious, the prior art must enable one skilled in the art to make and use the apparatus or method." *Motorola, Inc. v. Interdigital Technology Corp.*, 43 U.S.P.Q. 2d 1481, 1489 (Fed. Cir. 1997) (quoting *Beckman Instruments, Inc. v. LKB Produkter AB*, 13 U.S.P.Q. 2d 1301, 1304 (Fed. Cir. 1989)). Also, subsection 706.02(j) of the MPEP states that to establish a prima facie case of obviousness three criteria must be met:

(i) a suggestion or motivation to modify or combine references;

(ii) a reasonable expectation of success; and

(iii) all the limitations in the claim(s) must be taught or suggested by the reference, or combination of references.

Applicant respectfully asserts that nothing in the references cited by the Examiner, alone or in combination, describes, teaches, or suggests the combination of TRAIL with an antiprogestin such as Mifepristone as a chemotherapeutic composition. Nor is there any suggestion by the references that combining TRAIL with an antiprogestin would be effective in prostate cancer cells that are refractory to treatment by either TRAIL, or an antiprogetin, alone. As noted by the Examiner there is absolutely no teaching or suggestion in Bonavida, Yu, or Gliniak, of the combination of TRAIL with an antiprogestin such as Mifepristone to treat cancer. Office Action at page 13. Bonavida does describe a combination of TRAIL with actinomycin D (Act D), or cyclohexamide (CHX), or adriamycin (ADR). Each of these agents, however, function by completely different mechanisms than TRAIL. Thus, cyclohexamide is a general inhibitor of protein translation, Adriamycin D is an antibiotic with antineoplastic activity, and, actinomycin D is a transcriptional terminator that acts by binding to DNA between adjacent G-C pairs. The use of agents that act by different biochemical pathways is an

approach typically employed in combination therapy. In contrast, Applicant's invention employs a combination of two agents that act by the same, or by very similar, biochemical pathways to induce apoptosis. As described in Applicant's specification, both TRAIL and Mifespristone act via death domain receptors DR4 and DR5 to stimulate of caspase 8, which subsequently activates procaspases 3, 7, and 9. Applicant is therefore able to use Mifespristone to sensitize cells to TRAIL by activating the DR4/DR5 pathway. In this way, Applicant's methods maintains specificity for the TRAIL pathway for induction of cell death by an apoptosis-specific pathway. This is in contrast to the agents proposed by Bonavida which act by much more generalized mechanisms to induce cell death and thus, can result in non-specific side effects.

The Federal Circuit has held that the totality of a reference's teachings must be considered in finding whether the reference in fact suggests the invention in question, or teaches away from the invention in question. *W.L. Gore & Assocs. V Garlock, Inc.*, 220 USPQ 303, 311 (Fed. Cir. 1983). There is no suggestion in any of the references cited to combine TRAIL with another agent that acts by the TRAIL pathway to enhance the effectiveness of TRAIL. In fact, reading Bonavida, one would be discouraged from using a second agent of the TRAIL pathway in combination with TRAIL, as Bonavida describes using TRAIL with chemotherapeutics that work by different (and more generalized) biochemical pathways (e.g., actinomycin D, adriamycin, and cyclohexamide). Similarly, although Fathy El Etrby describes the use of Mifespristone in the treatment of prostate cancer, and Koide describes the use of Mifespristone to treat other types of cancer, there is absolutely no description of the use of Mifespristone to induce apoptosis in combination with TRAIL or that Mifespristone acts via the TRAIL pathway. Thus, there is no teaching or suggestion in Fathy El Etreby of using Mifespristone to induce DR5 receptors and/or caspase processing to thereby induce apoptosis.

It is well known in the field of cancer biology that a treatment that may work for one type of cancer is often ineffective for other types of cancers, and that even within a single cancer type, some cells may be refractory to treatment by a particular agent. Also, designing treatments for prostate cancer is complicated by the fact that prostate cells grow slowly (one reason the disease is seen in older men) and therefore, drugs

specifically directed towards cell growth are not very efficient in treating prostate cancer. Thus, as described in Applicant's specification, the challenge in prostate cancer is to develop agents that are effective in treating both androgen-sensitive prostate cells and androgen-insensitive prostate cancer cells. It is described in Applicant's specification that studies with TRAIL indicated that not all prostate cancer cells are sensitive to TRAIL (see Figure 1 of Applicant's specification). For example, as taught by Applicant's specification, TRAIL does not result in a significant increase in apoptosis and/or DR5 expression in certain androgen sensitive prostate cells (LNCaP). Also, such cells are not sensitive to Mifespristone at the levels used by Applicant (see the specification, FIG. 1A, 1C). Thus, Applicant respectfully asserts that the results of Gliniak and Koide using cancers that are not prostate cancer do not teach or suggest the use of TRAIL with another agent for treating prostate cancer. Nor do the studies of Yu indicate how TRAIL may be used to treat prostate cancer in those prostate cancer cells that are not sensitive to TRAIL. Nor do the studies of either Koide or Fathy El Etreby teach how Mifespristone and other antiprogestins may be used to treat prostate cancer cells that are refractory to Mifespristone.

Applicant respectfully asserts that the Examiner is applying the wrong standard of for determining obviousness. An invention may not be deemed obvious where the prior art only provides only an invitation to explore, and does not teach or suggest the Applicant's claimed invention. *In Ex parte Obukowicz*, 27 USPQ 2d 1063 (1992). Thus, whereas the references cited by the Examiner may have suggested the use of TRAIL in combination with other agents for treating prostate cancer, there is no suggestion to use TRAIL with an antiprogestin that activates the TRAIL pathway. Further, the courts have held that an obviousness rejection may not be predicated on the view that the invention was "obvious to try." *In re Lindell*, 385 F.2d 453 (CCPA 1967), and *Ex parte Levengood*, 28 USPQ 1300 (Bd. Pat. App. & Inter, 1993). Although both TRAIL and Mifespristone had been used individually with some efficacy in treating prostate cancer, there was no indication, based on the results in the cited art, that the combination of TRAIL and Mifespristone would induce apoptosis in prostate cancer cells, such as LNCaP prostate cancer cells, that are refractory to TRAIL alone.

For at least the above reasons, Applicant respectfully requests that the rejection under 35 U.S.C. § 103 be withdrawn.

CONCLUSION

In view of the foregoing amendment and remarks, each of the claims remaining in the application is in condition for immediate allowance. Accordingly, the Examiner is respectfully requested to reconsider and withdraw the outstanding rejections. The Examiner is respectfully invited to telephone the undersigned at (336) 747-7541 to discuss any questions relating to the application.

Respectfully submitted,

Date: January 21, 2005

Cynthia B. Rothschild (Reg. No. 47,040)

KILPATRICK STOCKTON LLP
1001 West Fourth Street
Winston-Salem, North Carolina 27101-2400
Phone: (336) 747-7541
Facsimile: (336) 607-7500

M0351-268908
WINLIB01:1112711.1